JUN 6 2000

NDA 12-154/S-024

Abbott Laboratories
Attention: Leslie Koehler
Manager, Regulatory Affairs
200 Abbott Park Road, D-389, AP3O
Abbott Park, IL 60064-3537

Dear Ms. Koehier:

Please refer to your supplemental new drug application dated July 24, 1998, received July 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ureaphil.

This supplemental new drug application provides for a labeling revision in response to the final rule, effective August 27, 1998, entitled *"Specific Requirements on Content and Format of Labeling for Human Drugs: Addition of Geriatric Use Subsection in the Labeling."* More specifically, the proposed labeling revision is as follows:

PRECAUTIONS section of the package insert, the following paragraph has been added:

> Geriatric Use: Ureaphil (Sterile Urea, USP) should not be infused in veins of the lower extremities of elderly patients. See **CONTRAINDICATIONS.**
>
> This drug is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. See **PRECAUTIONS.**
>
> In general, dose selection for an elderly patient should be cautious, generally starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling dated July 24, 1998.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 12-154/S-024." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MID 20857

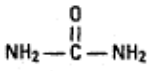
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

UREAPHIL®
Sterile Urea, USP
FOR RECONSTITUTION TO A 30% SOLUTION FOR INTRAVENOUS INJECTION
Single-dose Container

DESCRIPTION

Ureaphil (Sterile Urea, USP) is a synthetic urea prepared as a white, sterile, nonpyrogenic lyophilized powder for reconstitution with 5 or 10% Dextrose Injection, USP to provide a clear, colorless, hypertonic solution for intravenous infusion. Ureaphil is prepared as a solution and lyophilized in its final container.
Each 200 mL bottle of Ureaphil contains urea 40 g with citric acid, 1 mg added as a buffering agent
May contain sodium hydroxide for pH adjustment. 5130 mOsmol/liter (calc.) based on 40 g Ureaphil and 105 mL 5% dextrose injection to make a final volume of 135 mL 5326 mOsmol/liter (calc.) based on 40 g Ureaphil and 105 mL 10% dextrose injection to make a final volume of 135 mL
As determined by depression of freezing point, a theoretically isotonic solution of urea in water has a concentration of 1.63%.
Sterile Urea contains no bacteriostat or antimicrobial agent and is intended for use only after reconstitution as a single-dose injection. When smaller doses are required the unused portion should be discarded.
Ureaphil when reconstituted as a 30% solution of urea is a hypertonic osmotic dehydrating agent.
rea, USP, is the diamide of carbonic acid, chemically designated carbamide {CH_4N_2O), solid crystals, soluble in water. It has the following structural formula:



CLINICAL PHARMACOLOGY

The reduction of intracranial edema and abnormally elevated cerebrospinal fluid pressure which occurs following intravenous administration of hypertonic urea solutions, depends upon osmotic pressure gradients between the blood, extracellular and intracellular fluid compartments. Thus, the primary mechanism of action appears to be physical. Hypertonic urea rapidly increases blood tonicity thus effecting a greater urea concentration gradient in the blood than in the extravascular fluid. This results in transudation of fluid from the tissues, including the brain and cerebrospinal fluid into the blood.
As the concentration of urea in the glomerular filtrate increases, reabsorption of a proportional amount of water is prevented. Such retardation of proximal tubular reabsorption increases the rate and volume of urine flow.

INDICATIONS AND USAGE

When administered as a 30% solution, this preparation is indicated for the reduction of intracranial pressure (in the control of cerebral edema) and of intraocular pressure.

CONTRAINDICATIONS

Ureaphil (Sterile Urea, USP) should not be used in patients with severely impaired renal function, active intracranial bleeding or marked dehydration. Frank liver failure is also a contraindication for use.
Ureaphil should not be infused in veins of the lower extremities of elderly patients because phlebitis and thrombosis of superficial and deep veins may occur.

WARNINGS

1. Discard solution if not used within 24 hours after reconstitution.
2. Ureaphil (Sterile Urea, USP) may cause depletion of electrolytes which can result in hyponatremia and hypokalemia. Early signs of such depletion may indicate the need for supplementation before serum levels are reduced.
3. Extreme care is essential to prevent accidental extravasation of the solution at the site of injection since this may cause local reactions ranging from mild irritation to tissue necrosis.
4. If used in patients with some liver impairment, urea should be administered with great caution since there may be a significant rise in blood ammonia levels.

PRECAUTIONS

An indwelling urethral catheter should be used in comatose patients receiving urea for injection to insure bladder emptying.

Rapid intravenous administration of hypertonic solutions of urea may be associated with hemolysis as well as a direct effect on the cerebral vasomotor centers which may. result in increased capillary bleeding. These effects usually can be avoided by not exceeding an infusion rate of 4 mL per minute. Solutions of urea should not be administered through the same administration set through which blood is being infused.

Although arterial oozing has been reported as a nuisance when intracranial surgery is performed on patients following treatment with urea, it has not been a significant problem. However, sterile urea should not be used in the presence of active intracranial bleeding unless such use is preliminary to prompt surgical intervention to control hemorrhage. It should be kept in mind that reduction of brain edema induced by urea may result in reactivation of intracranial bleeding.

In the presence of kidney disease, urea should be administered with caution. Mild elevation of blood urea nitrogen does not preclude its use or continued use, but freouent laboratory studies should be made to determine if kidney function is adequate to eliminate the infused urea as well as that produced endogenously.

Patients exhibiting a temporary reduction in urine volume are generally able to maintain a satisfactory elimination of urea. However, if diuresis does not follow the injection of urea to such patients within 6 to 12 hours, the drug should be withdrawn pending further evaluation of renal function.

As with other infused solutions, Ureaphil (Sterile Urea, USP) may temporarily maintain circulatory volume and blood pressure in spite of considerable blood loss. Consequently, when excessive blood loss occurs within a short period of time, blood replacement should be adequate and simultaneous with the infusion of urea.

Hypothermia when used with urea infusion may increase the risk of venous thrombosis and hemoglobinuria.

Pregnancy Category C. Animal reproduction studies have not been conducted with Sterile Urea, USP. It is also not known whether sterile urea can cause fetal harm when given to a pregnant woman or can affect reproduction capacity. Sterile Urea, USP should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sterile urea is administered to a nursing mother

Geriatric Use: Ureaphil (Sterile Urea, USP) should not be infused in veins of the lower extremities of elderly patients. See CONTRAINDICATIONS.

This drug is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with unpaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. See PRECAUTIONS.

In general, dose selection for an elderly patient should be cautious, generally starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic. renal, or cardiac function, and of concomitant disease or other drug therapy.Do not administer unless seal of urea container is intact and reconstituted solution is clear. Discard unused portion.

ADVERSE REACTIONS

Headaches (reported to be similar to those which occur in some patients following lumbar puncture), nausea and vomiting, occasionally syncope and disorientation have been known to occur following intravenous administration. Less often reported is a transient agitated confusional state. No serious reactions have been noted when solutions have been infused slowly provided renal function is not seriously impaired or there is no evidence of active intracranial bleeding. Chemical phlebitis and thrombosis near the site of injection have been reported infrequently.

Reactions which may occur because of the solution (reconstituted) or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from-the site of injection, extravasation and hypervolemia.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

OVERDOSAGE

In the event of overdosage as reflected by unusually elevated blood urea nitrogen (BUN) levels, discontinue the drug, evaluate the patient and institute corrective measures as indicated. See PRECAUTIONS and DOSAGE AND ADMINISTRATION.

DOSAGE AND ADMINISTRATION

Ureaphil (Sterile Urea, USP) is administered as a 30% solution by slow intravenous infusion. The rate of injection should not exceed 4 mL per minute.

Sterile urea is prepared by adding an appropriate volume of 5 or 10% Dextrose Injection, USP. The desired diluent can be added directly to the urea container.

To prepare 135 mL of a 30% solution of sterile urea, the contents of one 40 g container are mixed with 105 mL of the diluent, or two such containers are mixed with 210 mL of diluent to prepare 270 ml of a 30% solution. Each milliliter of a 30% solution provides 300 mq of urea.

Ureaphil (Sterile Urea. USP) should be freshly prepared in each case. Discard any unused portion.

The amount to be administered is generally estimated on the basis of grams of urea per kilogram of body weight. Dosage also must take into account the clinical condition of the patient, especially the state of hydration, electrolyte balance and integrity of renal function. The total daily dose should not exceed 120 g of urea.

For the reduction of increased intracranial or intraocular pressure the adult dose ranges from I to 1.5 g (3.3 to 5 mL)per kilogram of body weight; or 0.45 to 0.68 g (1.5 to 2.3 mL) per pound of body weight.

In pediatric patients the dosage ranges from 0.5 to 1.5 g/kg of body weight. In infants up to 2 years of age as little as 0.1 glkg may be adequate.

Parenteral drug products (reconstituted) should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See PRECAUTIONS.

*HOW SUPP*LI*ED*

Ureaphil (Sterile Urea, USP) is supplied in a 200 mL single-dose glass container with 40 g of urea for reconstitution (List No. 1592).

Store at controlled room temperature 15 to 30°C (59 to 86°F).

ABBOTT LABORATORIES, NORTH CHICAGO. IL 60064 USA